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Basic Epidemiologic Considerations for Evaluating Associations between the Disinfection of Drinking Water and Cancer in Human Populations

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BASIC EPIDEMIOLOGIC CONSIDERATIONS FOR EVALUATING ASSOCIATIONS BETWEEN THE DISINFECTION OF DRINKING WATER AND CANCER IN HUMAN POPULATIONS

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16. ABSTRACT

This discussion concerns the basic epidemiologic considerations for evaluating studies which have reported associations between the disinfection of drinking water and cancer in human population. Recent epidemiologic studies are reviewed and evaluated according to these principals and concepts.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

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Introduction

An epidemiologist is primarily interested in the causes of disease. While experiments can be conducted in human populations to seek cures or preventives for disease, the epidemiologist in seeking causes of disease must rely upon data obtained from nonexperimental settings, as it is clearly unethical to knowingly cause illness or harm in studies of human populations. Thus, an epidemiologic study is nothing more than an attempt to describe nature, and the essential concern is with comparisons. Illness in an exposed group of individuals is compared with illness in an unexposed group, or the proportion of exposed individuals in a diseased group is compared with the proportion of exposed individuals in a group without the disease. Because of the largely unknown factors that lead to development of disease, an overriding consideration is comparability of the study groups. There is basically a lack of comparability in groups of individuals with and without specific characteristics, and it is essential in epidemiologic studies to collect and analyze data in a comparable manner. In experimental studies the investigator has the ability to assign exposure at random, and this tends to assure comparability over the long term.

The epidemiologist seeks to make a quantitative statement about the association between exposure and disease, and rates of similar types can be compared. The basic measures are the rate ratio or relative risk and rate difference or attributable risk, and they are

generally expressed as a point estimate (a single value) or as an interval estimate (a range of possible values consistent with the data). The appropriateness or accuracy of this measure is dependent upon components of study design, data collection, and analysis of epidemiologic data. These must be evaluated for each study, and the primary considerations are: 1) precision or lack of random error, and 2) validity or lack of systematic error. Precision is influenced primarily by the size of the study population and the efficiency of information obtained for each individual. An interval estimate is preferable to a point estimate because it accounts for random variability in the data. A point estimate is usually guaranteed to be wrong because it is only one point on an infinite scale of values. A point estimate does serve as an anchor point for a given confidence interval and is useful in that context. Assessing the validity of epidemiologic associations requires a search for potential sources of systematic bias which might have influenced the observed results. Both internal and external validity are important. Internal validity involves the making of a valid inference about the association between exposure and disease in a particular study and must be assured before considering external validity. External validity concerns extending the results of several studies to a target population and is often referred to as scientific generalization or interpretation. The results of epidemiologic studies must be interpreted in the context of other information, and no single study is likely to provide a definitive answer. The interpretation of epidemiologic data must be

cautious, as today's facts may become tomorrow's fallacies.[1] The interpretation of epidemiologic data requires an awareness by both epidemiologists and non-epidemiologists of the potential shortcomings of such data, and an assessment of the internal validity of each study must be undertaken. Internal validity has three basic components which should be considered, and each of these will be discussed in more detail later:

1. validity of selection of subjects (selection bias);
2. validity of information (information or observiation bias);
3. validity of comparison (confounding bias).

Conscientious investigators will discuss in their publications methods used to prevent selection bias, to minimize observation bias, to assess, prevent, and/or control confounding bias, and how these are likely to influence interpretation of the data.

Types of Epidemiologic Studies

To better understand the sources of potential bias which affect internal validity, it is necessary to have a basic understanding of the various types of epidemiologic studies. These are briefly reviewed according to a classification scheme proposed by Monson[1] (Table 1). In an experimental study the investigator randomly assigns exposure to a study participant, whereas in a nonexperimental study the investigator has no control over exposure. In a descriptive study information is available on exposure and disease for groups of

persons only, or information is available only on exposure or on disease. In an analytic study information on exposure and disease is available for each individual, and a measure of the association can be obtained. In a longitudinal study the time sequence between the exposure and disease can be inferred, but in a cross-sectional study the data on exposure and disease relate to the same point in time. In a case-comparison study individuals enter the study on the basis of disease and non-disease status, and various exposures are determined. In a cohort study individuals enter the study on the basis of exposure status. In a prospective cohort study the disease has not occurred at the time the exposed and nonexposed groups are defined. In a retrospective cohort study, the disease has occurred at the time the exposed and nonexposed groups are defined.[1]

I would classify as descriptive studies all of the early epidemiologic studies which report associations between cancer mortality and surface or chlorinated water because information was available on disease and exposure in groups of people rather than individuals. These studies have been extensively reviewed in the scientific literature[3-5] and at previous chlorination conferences.[6,7] Their shortcomings should be well known by now, and I feel no need to discuss them further. More recently, variations of traditional case-comparison and cohort study designs have been conducted. Several of the case-comparison studies using mortality data were reviewed by Cantor[7] at the last conference, and only those studies published in the peer-

reviewed literature since Cantor's review will be considered here. These include studies reported by Lawrence, et al.,[8] Wilkins and Comstock,[9] and Gottlieb, et al.[10]

Validity of Selection of Subjects

If the criteria used to enroll subjects in a study are not comparable, the data cannot be used to measure an association between exposure and disease because of selection bias. For selection bias to occur, the disease must have taken place prior to enrollment of the subjects in the study, and thus, it is important to consider selection bias in all case-comparison and retrospective cohort studies. In a case-comparison study, selection bias results from either selective admission of exposed persons into the diseased group, unexposed persons into the diseased group, exposed persons into the comparison group, or unexposed persons into the comparison group. In a retrospective cohort study, selection bias occurs when there is the selective admission of diseased persons into the exposed group or selective admission of nondiseased persons into the unexposed group. Selection bias can be prevented in case-comparison studies if knowledge of exposure is masked in selecting cases and comparison subjects and can be prevented in retrospective cohort studies if knowledge of disease is masked in selecting cohorts and determining exposure. Selection bias must be prevented, it cannot be controlled.[1]

There must be a difference in selection criteria between the two groups in order for selection bias to result. An inaccurate definition of disease or of exposure that applies equally to the two groups results in random misclassification, and this can only alter the results of a study toward no association between exposure and disease.[1]

Validity of Information

If data are collected on two groups using methods which are not comparable, the data contain incorrect information on the association between exposure and disease because of observation bias. In cohort studies observation bias results when information on disease outcome is obtained differently for exposed and nonexposed groups. In case-comparison studies observation bias results when information on exposure is obtained differently for cases and comparison subjects. A way to prevent observation bias in a cohort study is not to know the exposure status of study participants when information on disease is obtained, and any errors in measurement should be made equally in members of the exposed and nonexposed groups. In a case-comparison study, no observation bias is possible if neither the patient nor the data collector know the diagnosis when information on exposure is collected. However, this blindness is not always possible in a case-comparison study. To minimize observation bias in situations where the interviewer or patient knows case status, objectivity is sought in obtaining information. Questions are asked that require objective answers (close-ended) rather than subjective answers (open-

ended). This does not prevent observation bias but it tends to minimize it.[1]

Validity of Comparison

If a characteristic exists that is a cause of the disease and is also associated with the exposure and disease, the data relating exposure to disease may convey an appearance of association because of confounding bias. Although negative confounding can also occur, the primary concern is that confounding has led to the erroneous observation of an association. Confounding bias is potentially present in all epidemiologic data, and it must always be considered as the possible explanation for any association seen. Confounding bias does not result from any error of the investigator. It is a basic characteristic of any epidemiologic study.[1]

It is never possible to know all of the effects of confounding bias, but information can be collected on known or suspected confounding characteristics to prevent or control any bias introduced by those particular characteristics. If a characteristic can be made or demonstrated to have no association with exposure or with disease, that characteristic cannot be confounding. Matching is a technique generally employed in the study design to prevent confounding, and stratification or multivariate techniques are employed to assess and control confounding at the time of data analysis.

Measure of Association

As previously noted, it is important to measure the association between exposure and disease, and the usual measure is the rate ratio or relative risk. A rate ratio of unity (1.0) indicates no association and any other ratio indicates some association either positive or negative. Based on Monson's experience,[1] ranges of the rate ratio may be used to judge the strength of the association (Table 2). Any rate ratio between 0.9 and 1.2 indicates essentially no association. This is not to say that the true association is 1.0, but that associations in this range are generally considered too weak to be detected by epidemiologic methods. This means that if the exposure raises the rate of disease by 20 percent among the exposed nonexperimental epidemiologic methods are unlikely to detect this association. In situations where a true association is very weak, the range of variability in any data collected is large relative to the true rate ratio, and even with large numbers, random variation may lead to an observed rate ratio of 1.0. Similarly if the true rate ratio is 1.0, an observed rate ratio of 1.2 would not be unexpected because of random variation. Confounding bias is much more likely to influence the interpretation of small rate ratios. There may be one or more confounding factors that lead to a weak association between exposure and disease, and an epidemiologist is limited in his ability to identify and measure such weak confounding factors. Variability and confounding bias are much less likely to influence the interpretation of a large rate ratio when the association is based on reasonably

large numbers. It is generally accepted that if some confounding factor exists that accounts totally for such a strong assocation, its detection should be relatively simple. The size of a rate ratio, however, has little to do with the possibility that an association could be due to selection bias or observation bias. Either of these forms of bias can lead to a total misrepresentation of the underlying association between exposure and disease.

It should be noted that the ranges presented as a guide to the strength of an association are clearly arbitrary but are based on experience. However, two general points which Monson[1] suggests to keep in mind are accepted by most epidemiologists:

> "If the true association between exposure and disease is very weak, the detection of such an association by nonexperimental methods is unlikely.
>
> If the true association between exposure and disease is very strong, no epidemiologic expertise is necessary to detect it."

Interpretation of Epidemiologic Data Showing No Association Between Drinking Water Exposure and Cancer

The study by Lawrence, et al.[8] reported no association between trihalomethanes in surface water and cancer mortality. To interpret data reporting no association, it is important to detemine whether random misclassification could have resulted in not observing an

association when one was actually present. As previously noted, random misclassification results when there is imprecision in classifying study participant as diseased or nondiseased and exposed or unexposed and tends to alter a rate ratio towards unity (1.0). A rate ratio greater than 1.0 is lessened while one less than 1.0 is raised; with complete random misclassification the rate ratio is 1.0. Selection, observation, and confounding bias and random variability should also be considered, but random misclassification is always the important consideration when no association is reported in studies which are judged to have sufficient information and free of systematic bias.

The relation of trihalomethanes (THM) to colorectal cancer was evaluated by Lawrence, et al.[8] A total of 395 colorectal cancer deaths among white female teachers in New York State was compared to an equal number of deaths of teachers from noncancerous causes. Cumulative chloroform ($CHCl_3$) exposure was estimated by the application of a statistical model to operational records from the individual water treatment facilities that served the home and work addresses of each study subject during the 20 years prior to death. The odds of exposure to a surface source containing THM was no greater for cases than for controls (odds ratio = 1.07; the 90% confidence interval = 0.79, 1.43). The distribution of $CHCl_3$ exposure was not significantly different between cases and controls rated by Wilcoxon signed rank statistic. No effect of cumulative $CHCl_3$ exposure on

outcome was seen in a logistic analysis controlling for average source type, population density, marital status, age, and year of death. Misclassification of outcome was minimized by use of predominantly histogically confirmed cases of colorectal cancer and by searching the state tumor registry for possible cancer cases in the comparison group. Exposure misclassification was minimized by the collection of extensive records on home and work addresses, water treatment service areas, and estimates of THM exposure over the 20 year period prior to death, however, it is possible that exposures greater than 20 years may be important and this was not assessed. There appeared to be no selection or observation bias which might have been responsible for observing no association. In order to influence the results toward no association, the direction of bias would have to be opposite to the true association, and more complete information would have to have been collected for the comparison group. This seems unlikely. Potential confounding factors were assessed and controlled either in the study design by matching or in the analysis of the data. As with the other forms of bias, the direction of confounding must be opposite to the true association, and for this to bias the results negative confounding must have occurred. The search for negative confounding is usually of little value.[1] The authors thoroughly discussed possible sources of bias, methods for control, and possible effects on the interpretation of results. Since all measures of association are subject to random variation, it is not possible to completely rule out random variation

as a reason for no observed association. The study population was of reasonable size and the confidence interval for the odds ratio is narrow, but a more convincing case could be made for concluding that THM in chlorinated surface water are not associated with colorectal cancer if there were two or more studies where a rate ratio of 1.0 was found. The selection of comparison subjects is one of the most important aspects of a case-comparison study. Comparison subjects should be representative of the population from which cases are derived to avoid the selective admission of persons with specific diseases or exposures. Lawrence, et al.'s study population was basically homogenous, but most of the comparison group died of cardiovascular disease. There has been recent evidence from animal studies to suggest that cardiovascular disease may be associated with exposure to chlorine in drinking water where populations are deficient in calcium intake, and if this evidence applies to humans, the use of cardiovascular deaths as a comparison would tend to obscure a true association between THM and cancer mortality. This possibility should not be ruled out at the present time as a possible reason for no observed association.

Evaluation of precision or random variation is the primary consideration in interpreting results of the study conducted by Wilkins and Comstock[9] in Washington County, Maryland, to investigate the postulated relationship between organic chemical by-products of water chlorination and risk of human cancer. Vital records and

nonofficial census data available for each of nearly 31,000 study subjects were used to compute selected sex- and site-specific cancer incidence rates in a well-defined county population. Age, socio-economic status, smoking history, source of drinking water at home, and other individual characteristics of the study population were examined in relation to the cancer rates. Three historical cohorts, each distinguished by a different degree of exposure to chloroform and other chlorination by-products, were studied. Incidence rates for cancer of the bladder (relative risk = 1.80 95% confidence interval = 0.80, 4.75) among men and for cancer of the liver (relative risk = 1.80 95% confidence interval = 0.64, 6.79) among women were reported to be nearly two-fold higher in the drinking water cohort that had been supplied chlorinated surface water at home when compared to the cohort with a history of consumption of unchlorinated ground water. It is not felt that the results of this study can be interpreted as a true association because the reported rates are unstable and subject to random variation. There were few cancer deaths in the cohort, and the confidence intervals reported for the rate ratios are wide. Because the confidence intervals include 1.0, neither can the null hypothesis of no association be rejected. Random misclassification is not likely to have influenced the results toward no association, but because of the unstability of the rates, these results should be interpreted as inconclusive.

Interpretation of Epidemiologic Data Showing a Positive Association Between Drinking Water Exposure and Cancer

Selection, observation, and confounding bias and random variability should be considered as the reason(s) for the observed associations in the studies conducted by Gottlieb, et al.[10] Case-comparison mortality studies of 17 cancer sites (bladder, colon, kidney, liver, lymphoma, rectum, stomach, Hodgkin's lymphoma, leukemia, lung, malignant melanoma, multiple myeloma, prostate, breast, brain, esophagus, and pancreas) were conducted in 13 parishes (counties) of South Louisiana. Parishes were grouped for similarities in industrialization and approximate equal exposure to surface and ground water. Non-cancer deaths were randomly selected and matched to cancer deaths on age, gender, year of death, and parish where death occurred. Associations with exposure to chlorinated surface water (Mississippi River) compared with exposure to ground water were observed for cancer of the rectum in males (odds ratio = 3.18, 95% confidence interval = 1.96, 5.19) but not in females (odds ratio = 1.73, 95% confidence interval = 0.97, 3.10) when lifetime water use was considered. Lifetime water use was defined as type of water used by cases and comparison subjects at birth and at death, and the analysis was confined to those subjects where surface water was used at both birth and death or ground water was used at both birth and death. Associations which were not observed for cancer sites such as bladder, colon, kidney, liver, and stomach must be interpreted in light of the previous discussion of random misclassification of exposures, since water exposures for study subjects

could not be traced for more than ten years and lifetime exposures were estimated by classification of water source only at birth and death. The association seen for cancer of the rectum in males must be interpreted in light of a possible bias in selection of cases and comparison subjects, observation bias, or confounding bias. Because data were available on both disease and exposure when subjects were selected, selection and observation bias were possible. The effect of these possible sources of bias could not be adequately assessed because control measures were inadequately discussed in the publication. Confounding bias was controlled to the extent possible for factors which could be readily obtained from death certificates (gender, race, age, year of death were controlled by matching and data were obtained on occupation and ancestry). However, it was not possible to accurately assess individual occupational exposures, and occupation may be a possible confounding bias which contributed to the association observed for cancer of rectum in males and not observed for females. There is also the possibility that this association was observed because of random variability due to a possible multiple comparison problem. Gottlieb, et al.[10] suggested that the multiple comparison problem is minimized because each case-comparison series was selected independently within the study population, but the degree to which these may be independent observations can be questioned. The studies were conducted within the same, small geographic area, and the multiple comparison problem still exists within each series of observations.

Summary

It must be recognized that all epidemiologic data are imperfect no matter what their source or how they were collected. There are few absolutes. Few sets of epidemiologic data are worthless and few convey absolute truth. The task is to decide how to judge the validity of the data. Any judgement must consider not only the potential for bias but also how bias might have contributed to the observed association (would the true association likely be altered toward no observed association or how likely is the observed association a true association). The source of the data may not be ideal, but it may be the only source available. The data may not have been collected under absolutely correct circumstances, but the error introduced may be small. The analysis of the data may have been superficial but further analysis may add little to the understanding of the meaning of the association seen. The interpretation of the meaning of the association must take into account the source of the data, methods of collection of information, and methods of analysis. This is largely a scientific process, but decisions as to the utility of the data are generally based on an independent process that is primarily political.[1]

In summary, the large number of epidemiologic studies conducted to date suggest that there may be an association between exposure to surface waters that have been chlorinated and mortality due to one or more cancer sites. However, these studies have done little to clarify

the specific association(s) and the possible magnitude of the association. Because of their design, the two case-comparison studies of incident cases of bladder cancer and colon cancer to be presented at this session by Cantor and by Cragle should be able to shed some light on this subject.

In abstracts prepared for this conference, Cantor reports an association between bladder cancer and use of a chlorinated surface water, and Cragle reports an association between colon cancer and home consumption of chlorinated water. In a case-comparison study of 2982 incident cases of bladder cancer and 5782 population-based comparison subjects from ten areas of the United States, a relative risk of 3.1 (confidence interval = 1.5, 6.5) was observed by Cantor in nonsmokers who had used chlorinated surface water for 60 or more years compared to nonsmokers who had never used surface or chlorinated water. In a case-comparison study of 200 incident cases of colon cancer and 407 hospital-comparison subjects among North Carolina white residents, Cragle observed odds ratios of 1.38, 2.15, and 3.36 for home consumption of chlorinated water for 16 or more years and colon cancer in 60, 70, and 80 year olds. These studies are suggestive of an association between bladder and colon cancer and consumption of chlorinated water over a long period of time in nonsmokers and for a moderate period of time in an elderly population, but additional case-comparison studies are required before conclusions can be extended to other populations. Retrospective cohort studies should also be conducted where suitable

cohorts can be assembled and followed. Both of these study designs, however, require an accurate assessment of past exposure to contaminants of interest for a sufficient length of time (which may be greater than 20 years) to minimize random misclassification.

This paper was based largely on concepts and principals discussed by Monson either in his lectures or in his book,[1] and no claim is made by the author for the originality of these principals and concepts. In several instances the statements are paraphrased or taken directly from Monson's work, as I know of no better way to present or state these principles. The review of the published works[8-10] are, however, solely the opinion of the author.

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TABLE 1

Types of Epidemiologic Studies*

- I. Experimental
- II. Nonexperimental
  - A. Descriptive
  - B. Analytic
    - 1. Longitudinal
      - a. Cohort or Follow-up
        - (1) Prospective
        - (2) Retrospective
      - b. Case-Comparison
    - 2. Cross-Sectional

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TABLE 2

A Guide to Strength of Association*

Rate Ratio		Strength of Association
0.9 - 1.0	1.0 - 1.2	None
0.7 - 0.9	1.2 - 1.5	Weak
0.4 - 0.7	1.5 - 3.0	Moderate
0.1 - 0.4	3.0 - 10.0	Strong
<0.1	<10.0	Infinite

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